REMARKS

Claims 1-38 were pending the application. Claims 1-24 and 35-38 have been canceled, without prejudice, as being directed to a non-elected invention. Claims 25, 27, 29, and 34 have been amended. Accordingly, upon entry of this amendment, claims 25-34 will be pending. For the Examiner's convenience, the pending claims are set forth in Appendix A.

Support for the amendments to the claims may be found, at least, in the specification and claims as originally filed.

No new matter has been added. Any amendments to and/or cancellation of the claims should in no way be construed as an acquiescence to any of the Examiner's rejections and was done solely to more particularly point out and distinctly claim the subject matter of Applicants' invention in order to expedite the prosecution of the application. Applicants reserve the right to pursue the claims as originally filed in this or a separate application(s).

Priority

With respect to the priority claim for the instant application, the Examiner has indicated that

> [t]he instant application is granted the benefit of priority for the U.S. Provisional Application Nos. 60/141,031, filed on June 25, 1999, 60/142,690, filed on July 1, 1999, and 60/151,251, filed on August 27, 1999 as requested in the declaration and the first lines of the specification. The instant application is not granted the benefit of priority for the 12 foreign applications filed in Germany as requested in the declaration because the instant application does not comply with the rules set out in 35 U.S.C. 119 (a)–(d): namely, the foreign application was filed more than 12 months before the U.S. filing date and/or a certified copy of the original foreign application has not been filed with the Office. Applicants are requested to comply with these rules, if possible, or withdraw claims to priority benefits.

Applicants respectfully submit that Applicants intend to file certified copies of the original foreign applications to which the instant application claims priority.

Information Disclosure Statement

With respect to the Information Disclosure Statement for the instant application, the Examiner has indicated that "[n]o information disclosure statement has been filed with the instant application as of the date mailed of the instant Office Action." Applicants respectfully submit that Applicants intend to file an Information Disclosure Statement for the instant application.

Objections to the Specification

The specification is objected to by the Examiner because, according to the Examiner, the title is not descriptive. The Examiner suggests the following new title: — Methods of Producing a Fine Chemical Using a Glucose Resistance Amylase Regulator protein from *Corynebacterium glutamicum*—

Applicants have amended the title pursuant to the Examiner's suggestion. Accordingly, Applicants respectfully request reconsideration and withdrawal of the foregoing objection to the title.

The Abstract is objected to by the Examiner for "containing the abbreviation MR" without definition." The Examiner is of the opinion that "[t]his abbreviation would be wholly unclear without reading the description, which is not as universally available."

Applicants have amended the Abstract to include the definition of the abbreviation "MR". Accordingly, Applicants respectfully request reconsideration and withdrawal of the foregoing objection to the Abstract.

The specification is objected to by the Examiner because "[o]n page 2, line 34, the term "e.g." is listed with no examples following it."

Applicants have amended the specification to remove the term "e.g." at the position indicated by the Examiner. Accordingly, Applicants respectfully request reconsideration and withdrawal of the foregoing objection to the specification.

Furthermore, the Examiner has objected to the specification because "[i]n Table 4, the % homology is in the tens of thousands while percent is a range from 1-100."

Applicants respectfully submit that at page 57, lines 2-3, it is explained that in Table 4, a ',' represents a decimal point. For example, a value of "40,345" in this column represents "40.345%". Accordingly, Applicants respectfully request reconsideration and withdrawal of the foregoing objection to the specification.

The Examiner has objected to the specification because, according to the Examiner, "[t]he specification is confusing in Table 1; the assignment of functionality is wholly unclear. For example, in Table 4, the assignment of function is clear. No sources or procedures are named for the sequences in Table 1."

Applicants respectfully submit that Table 1 is clear in that the assignment of functionality is clearly set forth for each molecule. Applicants respectfully submit that sources or procedures are not required in order to indicate the activity of each molecule, as determined by Applicants. Accordingly, Applicants respectfully request reconsideration and withdrawal of the foregoing rejection.

Claim Objections

Claim 29 is objected to for a typographical error. On page 2, the comma between *Corynebacterium* and *lilium* is inappropriate.

Applicants have amended the typographical errors in claim 29. Accordingly, Applicants respectfully request reconsideration and withdrawal of the foregoing objection to claim 29.

Rejection of Claim 29 Under 35 U.S.C. §112, Second Paragraph

The Examiner has rejected claim 29 under 35 U.S.C. § 112, second paragraph, "as being indefinite for failing to particularly point out and distinctly claim the subject

matter which applicant regards as the invention." In particular, the Examiner is of the opinion that

> several of the names are inappropriate members of the Markush group because they either are aliases or cannot be found in the art as a recognized species:
>
> a) *Corynebacterium lilium* is an alias for *Corynebacterium glutamicum*
> b) *Corynebacterium acetophilum* is an unknown species
> c) *Brevibacterium ammoniagenes* is an alias for *Corynebacterium ammoniagenes*
> d) *Brevibacterium divaricatum* is an alias for *Corynebacterium glutamicum*
> e) *Brevibacterium flavum* is an alias for *Corynebacterium glutamicum*
> *f) Brevibacterium lactofermentum* is an alias for *Corynebacterium glutamicum*
> g) *Brevibacterium paraffinolyticum* is an unknown species.
>
> Also, in Table 3, generic *Brevibacterium* species and *Corynebacterium* species are noted, but their definition is unclear.

Applicants respectfully traverse the foregoing rejection. However, in the interest of expediting prosecution of the application, and in no way acquiescing to the Examiner's rejection, Applicants have amended claim 29 to delete the terms *Brevibacterium lactofermentum, Brevibacterium divaricatum, Brevibacterium ammoniagenes, Corynebacterium lilium, Brevibacterium paraffinolyticum,* and *Brevibacterium flavum.*

With respect to part b) of the Examiner's rejection, Applicants respectfully submit that *Corynebacterium acetophilum* is a known species. As evidence of this, Applicants submit herewith, as Appendix A, the abstract of a reference which describes use of the *Corynebacterium acetophilum* species (Murooka Y, *et al.* (1977) *J Bacteriol.*130(1):62-73).

With respect to the Examiner's statement that "generic *Brevibacterium* species and *Corynebacterium* species are noted, but their definition is unclear," Applicants respectfully submit that *Brevibacterium* and *Corynebacterium* are clearly well known in the relevant art. Accordingly, the meaning of these terms would be readily apparent to

one of skill in the art after reading the instant application. Furthermore, breadth of a claim may not be equated with indefiniteness (MPEP §2173.04). Accordingly, for the reasons set forth above, Applicants submit that the terms *Brevibacterium* and *Corynebacterium* are clear and definite and therefore Applicants respectfully request reconsideration and withdrawal of the foregoing rejection.

Rejection of Claim 31 Under 35 U.S.C. §112, Second Paragraph

The Examiner has rejected claim 31 under 35 U.S.C. § 112, second paragraph, "as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention." In particular, the Examiner is of the opinion that "[t]he Markush member "enzymes" as a fine chemical is confusing. While amino acids can be considered fine chemicals, an assembly of amino acids into the form of a protein/enzyme is not considered a fine chemical. Such a definition is repugnant in the art."

Applicants respectfully traverse the foregoing rejection. Applicants respectfully submit that an enzyme may be considered a fine chemical. Hawley's Condensed Chemical Dictionary (13^{th} ed. 1997), defines the term "fine chemical" as follows: a chemical produced in comparatively small quantities and in a relatively pure state. Examples are pharmaceutical and biological products, perfumes, photographic chemicals, and reagent chemicals. Accordingly, based on this definition, a fine chemical may include any biological product, and is not limited to amino acids, for example, as suggested by the Examiner. Accordingly, for the reasons set forth above, Applicants respectfully request reconsideration and withdrawal of the foregoing rejection.

Rejection of Claim 34 Under 35 U.S.C. §112, Second Paragraph

The Examiner has rejected claim 34 under 35 U.S.C. § 112, second paragraph, "as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention." In particular, the Examiner is of the opinion that "[i]t is confusing how the introduction of the complement of a coding sequence can effect the production of a fine chemical. The disclosure describes SEQ ID

NO:1 as a coding sequence of a glucose resistance amylase regulator. It is unclear how the complement of this gene, when introduced into the genome of a host cell, could be productive."

Applicants respectfully traverse the foregoing rejection. As the Examiner is undoubtedly aware, genomic DNA is routinely double stranded, the gene expressed therein including both a coding strand and a complementary strand. Accordingly, it is Applicants' position that the recitation of "a complement thereof" in claim 34 would have a clear meaning to the skilled artisan. However, in an effort to expedite prosecution of the application, and in no way acquiescing to the Examiner's rejection, claim 34 has been amended such that it no longer refers to the complement of SEQ ID NO:1. Accordingly, Applicants respectfully request reconsideration and withdrawal of the foregoing rejection to claim 34.

The Examiner further rejected claim 34 under 35 U.S.C. § 112, second paragraph, "as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention" because, according to the Examiner, "[t]he term "about" in claim 34 is a relative term, which renders the claim indefinite. The term "about" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention."

Applicants respectfully traverse the foregoing rejection. However, in an effort to expedite prosecution of the application, and in no way acquiescing to the Examiner's rejection, claim 34 has been amended such that it no longer recites the term "about." Accordingly, Applicants respectfully request reconsideration and withdrawal of the foregoing rejection to claim 34.

Rejection of Claims 25-34 Under 35 U.S.C. §112, First Paragraph

The Examiner has rejected claims 25-34 under 35 U.S.C. § 112, first paragraph, written description, "as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that

the inventor(s), at the time the application was filed, had possession of the claimed invention." In particular, the Examiner is of the opinion that

> [a]lthough the species of glucose resistance amylase regulator SEQ ID NO:2 is discussed in the specification, there is no clear evidence that this sequence is a glucose resistance amylase regulator. No testing of activity is disclosed; no homology alignments are offered. Thus, without a clear function of the disclosed sequence, the characteristics of the sequence are inadequately described in the instant specification as originally filed. To satisfy the written description aspect of 35 U.S.C. § 112, first paragraph, for a claimed genus of molecules, it must be clear that: (1) the identifying characteristics of the claimed molecules have been disclosed, e.g., structure, physical and/or chemical characteristics, functional characteristics when coupled with a known or disclosed correlation between function and structure, or a combination of these; and (2) a representative number of species within the genus must be disclosed. In this case, item (1) is not met. If Applicants can convincingly demonstrate that SEQ ID NO:1 particularly encodes a glucose resistance amylase regulator, for example, by significant homology alignment, this portion of the rejection would be withdrawn. In addition to the above written description issue, the instant claims are rejected based on their open claim language in the absence of the disclosure of full-length genes. The instant claims are drawn to methods using a nucleotide sequence *comprising* SEQ ID NO:1; the open claim language reads on the use of the full-length gene. SEQ ID NO:1 is not a full-length open reading frame based on the absence of a real start and stop codon and based on the small size of the encoded protein relative to other art. Insofar as the disclosed polynucleotide sequence directly encodes the entire functional portion of a glucose resistance amylase regulator, the instant specification provides adequate written description.

With respect to claim 34, the Examiner is of the opinion that

> [c]laim 34 is also rejected based on its claiming the use of polynucleotides described by variable structure without function. The instant specification discloses polynucleotides with at least 60% with SEQ ID NO: 1. Applicants have fully described the genus relating to said SEQ ID NOs with both sequence identity limitations and functional limitations (i.e., having glucose resistance

> amylase regulator, provided that this is a real function of the encoded polypeptide, as noted above). However, the genus of the instant claims also contains polynucleotides within the sequence identity limitations, but having different function. Applicants have not fully described a genus that has sequence identity limitations in the absence of functional limitations.

Applicants respectfully traverse the foregoing rejection. Applicants respectfully submit that there is sufficient written description in Applicants' specification regarding the claimed methods for producing a fine chemical, to inform a skilled artisan that Applicants were in possession of the claimed invention at the time the application was filed. Claim 25 is directed to methods for producing a fine chemical, comprising culturing a cell containing a vector comprising the nucleotide sequence of SEQ ID NO:1 such that the fine chemical is produced. Claim 34 is directed to methods for producing a fine chemical, comprising culturing a cell whose genomic DNA has been altered by the inclusion of an isolated nucleic acid molecule selected from the group consisting of: a nucleic acid molecule comprising a nucleotide sequence which is at least 90% identical to the nucleotide sequence of SEQ ID NO:1, and encodes a polypeptide which has glucose resistance amylase regulator activity; a nucleic acid molecule comprising a fragment of at least 30 nucleotides of a nucleic acid comprising the nucleotide sequence of SEQ ID NO:1, and encodes a polypeptide which has glucose resistance amylase regulator activity; a nucleic acid molecule which encodes a polypeptide comprising an amino acid sequence at least 90% identical to the amino acid sequence of SEQ ID NO:2 and has glucose resistance amylase regulator activity; and a nucleic acid molecule which encodes a fragment of a polypeptide comprising the amino acid sequence of SEQ ID NO:2 and has glucose resistance amylase regulator activity, wherein the fragment comprises at least 10 contiguous amino acid residues of the amino acid sequence of SEQ ID NO:2.

Claim 25 is directed to use of the entire sequence of SEQ ID NO:1 for the production of fine chemicals. The structure of this molecule, *e.g.*, the full sequence of the molecule, is fully described by Applicants' specification. A clear function of this molecule, *e.g.*, as a glucose-resistance amylase regulator, is also described in Applicants' specification. Claim 25 is limited to the culturing a cell containing a vector comprising

the nucleotide sequence of SEQ ID NO:1 ***such that the fine chemical is produced.*** SEQ ID NO:1 contains sufficient sequence information to encode the specified activity, *e.g.*, glucose resistance amylase regulator activity. Accordingly, Applicants respectfully submit that SEQ ID NO:1 is adequately described by Applicants' specification.

With respect to claim 34, in Example 15 of the *Interim Guidelines for Examination of Patent Applications Under the 35 U.S.C. §112, First Paragraph Written Description Requirement* the "theoretical specification" discloses a messenger RNA sequence, SEQ ID NO:1, which encodes a human growth hormone. The "theoretical specification" claims antisense molecules that inhibit the production of human growth hormone. The Guidelines provide that

> [c]onsidering the specification's disclosure of (1) ***the sequence (SEQ ID NO:1) which defines and limits the structure of any effective molecules such that one skilled in the art would be able to immediately envisage members of the genus embraced by the claim*** and 2) the functional characteristics of the claimed invention as well as a routine art-recognized method of screening for antisense molecules which provide further distinguishing characteristics of the claimed invention, along with, 3) the general level of knowledge and skill in the art, one skilled in the art would conclude that applicant was in possession of the invention.....***the claimed invention is adequately described. (Emphasis added).***

Similar to Example 15 of the *Interim Guidelines*, the instant specification describes the methods of using the nucleotide sequence of the nucleic acid molecules of the invention (SEQ ID NOs:1) ***which define and limit the structure of any nucleotide fragments such that one skilled in the art would be able to immediately envisage members of the genus embraced by the nucleotide fragment claims***. Thus, based on the *Written Description* guidelines, the invention claimed in claim 34 is adequately described.

Furthermore, Example 14 of the *Revised Interim Written Description Guidelines Training Materials* provides that a claim directed to variants of a protein having SEQ ID NO:3 "that are at least 95% identical to SEQ ID NO:3 and catalyze the reaction of A→B"

with an accompanying specification that discloses a single species falling within the claimed genus, satisfies the requirements of 35 U.S.C. §112, first paragraph for written description. The rational behind the foregoing conclusion, as presented by the *Written Description Guidelines*, is that "[t]he single species disclosed is representative of the genus because all members have at least 95% structural identity with the reference compound and because of the presence of an assay which Applicant provided for identifying all of the at least 95% identical variants of SEQ ID NO:3 which are capable of the specified catalytic activity."

Similarly, in the present case, claim 34 is directed to methods for producing a fine chemical using an isolated nucleotide sequence that is at least 90% identical to the amino acid sequence shown in SEQ ID NO:1, wherein the nucleotide sequence encodes a polypeptide which has glucose-resistance amylase regulator activity. Thus, based on the teachings in Applicants' specification, one of skill in the art would conclude that Applicants were in possession of the claimed invention at the time of filing.

Based on the foregoing teachings in Applicants' specification and the knowledge generally available in the art, one skilled in the art would conclude that Applicants were in possession of the claimed invention at the time of filing of the application. The skilled artisan would also be able to make and use the claimed polypeptide fragments using only routine experimentation.

Accordingly, based on the amendments to the claims and the comments set forth above, Applicants respectfully request reconsideration and withdrawal of the foregoing 35 U.S.C. § 112, first paragraph rejection.

Rejection of Claims 25-34 Under 35 U.S.C. §101

Claims 25-34 are rejected under 35 U.S.C. §101 because, according to the Examiner, "the claimed invention is not supported by either an asserted utility or a well-established utility." In particular, the Examiner is of the opinion that "the function of the encoded protein, glucose resistance amylase regulator, is not convincing given the disclosure. Without a known function, it is unclear how to use such a polynucleotide or such a method using a polynucleotide, i.e., what fine chemical to produce?"

Applicants respectfully traverses the foregoing rejection. Applicants asserts that a specific, substantial and well-established utility, which would have been credible to one skilled in the art at the time of the invention, is clearly disclosed in the instant specification.

The molecules described in Applicants' specification are metabolic regulatory (MR) polypeptides. The claimed methods for producing fine chemicals utilize MR polynucleotides and polypeptides (*e.g.,* polynucleotides and polypeptides having the sequences of SEQ ID NO:1 and SEQ ID NO:2) which have glucose resistance amylase regulator activity as described in the instant application. Applicants have described the chemical, physical and the functional characteristics of the MR polypeptides, *e.g.,* the glucose resistance amylase regulator polypeptides used in the methods of the invention, in the instant specification, including, for example, in Table 1.

Furthermore, the specification teaches the activities of the MR polypeptides at, for example, page 8, line 30, through page 9, line 3, as set forth below:

> [t]he molecules of the invention may be utilized in the modulation of production of fine chemicals from microorganisms, such as *C. glutamicum*, either directly (*e.g.*, where modulation of the activity of a lysine biosynthesis regulatory protein has a direct impact on the yield, production, and/or efficiency of production of lysine from that organism), or may have an indirect impact which nonetheless results in an increase in yield, production, and/or efficiency of production of the desired compound (*e.g.*, where modulation of the regulation of a nucleotide biosynthesis protein has an impact on the production of an organic acid or a fatty acid from the bacterium, perhaps due to concomitant regulatory alterations in the biosynthetic or degradation pathways for these chemicals in response to the altered regulation of nucleotide biosynthesis).

As the Examiner is aware, the applicant does not have to provide evidence sufficient to establish that an asserted utility is true "beyond reasonable doubt." *In re Irons*, 340 F.2d 974, 978, 144 USPQ 351, 354 (CCPA 1965). Instead, evidence will be sufficient, if considered as a whole, it leads a person of ordinary skill in the art to conclude that the asserted utility is more likely than not true. M.P.E.P. §2164.07. Based

on the teachings in Applicants' specification regarding the activity of the molecules used in the methods of the invention, Applicants respectfully submit that a person of ordinary skill in the art would conclude that Applicants' asserted utility is more likely than not true, which is all that is required under 35 U.S.C. §101.

In view of all of the foregoing, Applicants asserts that the utilities set forth in the specification for the invention as instantly claimed are specific, credible and substantial and/or well-established utilities that would have been recognized as such by one of skill in the art at the time the application was filed. Therefore, the instant claims meet the requirements of 35 U.S.C. §101, and Applicants respectfully request reconsideration and withdrawal of this rejection.

Rejection of Claims 25-34 Under 35 U.S.C. §112, First Paragraph

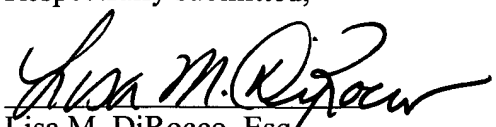
Claims 25-34 are also rejected under 35 U.S.C. §112, first paragraph, enablement. Specifically, since the claimed invention is not supported by either an asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

Applicants respectfully traverse the foregoing rejection. As set forth above, the claimed invention has specific, substantial, and credible utilities and, thus, one of skill in the art would know how to use the claimed invention.

SUMMARY

If a telephone conversation with Applicants' Attorney would expedite the prosecution of the above-identified application, the examiner is urged to call the undersigned at (617) 227-7400.

Respectfully submitted,



Lisa M. DiRocco, Esq.
Registration No. 51,619
Attorney for Applicants

LAHIVE & COCKFIELD, LLP
28 State Street
Boston, MA 02109
Tel. (617) 227-7400

Dated: **August 11, 2003**